Chapter 9

Pulmonary Arterial Hypertension associated with Isolated Atrial Septal Defect: the role of *BMPR2*-mutations and outcome after defect closure

M.T.R. Roofthooft, W.S. Kerstjens-Frederikse, J.M. Douwes, K. Pricker, B. Bartelds, Y.J.Vos, F.J. Meijboom, H.L. Hillege, R.M.F. Berger

Submitted

ABSTRACT

Background: Little is known about the factors that contribute to the development of pulmonary arterial hypertension (PAH) in adult patients with atrial septal defect (ASD). The goal of this study was to identify clinical and genetic risk factors for the development of PAH and to define predictors of PAH resolution after defect closure.

Methods: In a retrospective study, 1203 patients with isolated ASD were included from the Dutch nationwide registry of adult patients with congenital heart defects.

Results: Seventy-one patients had PAH (6%). Sinus venosus type ASD and time span of unrepaired ASD were associated with PAH. In a study of 68 of the ASD patients with PAH and 186 controls without PAH, matched for gender, ASD-type and time span of unrepaired ASD, the size of the ASD was identified as an additional risk factor for PAH. Three patients with PAH were excluded because of incomplete data. DNA samples were available in 56 of the 68 ASD-PAH patients but *BMPR2* mutation analysis revealed no mutations. The NYHA functional class was worse and mortality higher in patients with PAH ($p < 0.05$). Defect closure was performed in 44 of the 68 patients with ASD-PAH. In 27 patients (61%) PAH resolved after repair. No pre-operative clinical or hemodynamic characteristics could be found that predict postoperative PAH-resolution.

***Conclusions*:** PAH occurred in 6% of patients with ASD. Sinus venosus type defect, larger size of ASD and an older age at ASD-repair were associated with PAH. Gender and the presence of *BMPR2* mutations were not associated with PAH. Thirty-nine percent of the patients had persistent PAH after closure, but these patients could not be identified from their pre-operative clinical and hemodynamic characteristics. Functional class improved in all patients after closure of the defect irrespective of PAH.

INTRODUCTION

The natural course of hemodynamically significant atrial septal defects (ASDs) is complicated by right ventricular failure (RVF), arrhythmias and pulmonary arterial hypertension (PAH).[1-6] The occurrence of PAH in association with ASD leads to increased morbidity and decreased life expectancy and can be prevented by timely closure of the defect by surgical or transcatheter procedures. PAH has been reported to develop in 10-30% of untreated ASD patients, most frequently in the 2nd and 3rd decade of life.[2, 7-11] Previously reported risk factors for the development of PAH in these patients include being female, size and type of defect and age at defect closure. However, these known risk factors do not sufficiently explain why only a minority of ASD patients develop PAH, nor do they allow for the identification of ASD patients who will develop PAH.[6, 9, 12, 13] Increased genetic susceptibility due to the presence of a mutation in the bone morphogenetic protein receptor 2 (*BMPR2*) gene in combination with increased pulmonary blood flow due to the ASD acting as a "second hit" to the pulmonary vasculature has been proposed as a potential explanation.

Patients with ASD and associated PAH often do not present with typical Eisenmenger syndrome with a reversed shunt through the defect, but rather with sub-systemic pulmonary vascular resistance and residual left to right shunting through the defect. We do not know what the best way is to treat these patients. ASD closure in the presence of PAH has been reported to be beneficial in the short term. However, concerns remain regarding the potential progression of PAH over time and an eventual unfavourable outcome.

The purpose of this study was to investigate the role of *BMPR2* mutations and clinical risk factors in 71 ASD-PAH patients enrolled in a Dutch registry for adults with congenital heart diseases. Further, we aimed to describe outcomes for patients with PAH after ASD closure, and to identify predictors of either PAH-resolution or persistence after defect closure.

PATIENTS AND METHODS

Patients with isolated ASD were selected from the CONCOR registry, a nationwide Dutch registry of adult patients (age ≥ 18 years) with congenital heart defects using diagnostic codes defined by the Association for European Paediatric Cardiology since 2005 - International Paediatric and Congenital Code (IPCCC; http://www.IPCCC.net): ASD within oval fossa and secundum ASD (05.04.02); sinus venosus ASD (05.05.00); superior sinus venosus ASD (05.05.01); inferior sinus venosus ASD (05.05.02); and AVSD, isolated atrial component: Primum ASD (06.06.01). This registry, initiated in 2000, is a platform for studying the epidemiology of congenital heart defects.[14] Written informed consent for using clinical data and DNA anonymously for research was obtained from all patients at the time of their inclusion in the CONCOR registry.

Patients with PAH were identified by either right heart catheterization (RHC) or echocardiography. Pulmonary hypertension was defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg in the absence of a pulmonary wedge pressure (PWP) ≥ 15 mmHg at RHC and/or a right ventricular systolic pressure (RVSP) ≥ 40 mmHg at echocardiography, as previously described by Duffels et al.[15]

RVSP was corrected for additional pulmonary valve stenosis. Clinical characteristics, including those that have previously been suggested to be associated with PAH, were also collected.

A case-control study was performed to identify additional risk factors such as the presence of a *BMPR2* mutation, size of ASD, New York Heart Association (NYHA) functional class at time of ASD diagnosis and hemodynamic parameters. Controls were matched for gender, type of ASD and time span of unrepaired ASD. Matching was applied following a 1 to 2.7 ratio, which was defined as the age of patients with an unrepaired ASD to age at ASD closure in patients who had had a repair. Patient history, use of medication, co-morbidity and hemodynamics (RHC, echocardiography) were collected from medical charts.

Mutation analysis of the *BMPR2* gene was performed in 56 out of the 68 PAH patients using Denaturing Gradient Gel Electrophoresis (DGGE) analysis, followed by direct sequencing of fragments showing an aberrant DGGE pattern. Exon 1 was routinely analyzed by direct sequencing.[16] To analyze the 13 exons of the gene, 24 primer-pairs were designed as described by Wu et al.[17] All fragments were amplified using a single PCR program. Primer sequences, PCR and DGGE conditions are available upon request. For detecting deletions or duplications of whole exons, we used the Multiple Ligation-dependent Probe Amplification kit P093-HHT (MRC-Holland, Amsterdam, the Netherlands).

Outcome was defined as the resolution of PAH after defect closure, functional status (NYHA class) at last visit and survival period. The pulmonary artery pressure was measured by RHC or RVSP was assessed at echocardiography, as previously described. The median follow-up time was defined as the time interval between ASD diagnosis and the last follow-up visit.

Statistical methods

Data analysis was performed using SPSS software (version 16; SPSS 2007, Chicago, Illinois, USA). Variables are presented as n (%) for categorical and ordinal variables or median (interquartile range) for continuous, not normally distributed, variables. Comparisons were made using the Chi square test (independent variables) for categorical variables and Student-t and Wilcoxon Signed Rank tests, where appropriate, for continuous and ordinal variables. Survival was analysed using Kaplan-Meier curves with log rank test and Cox regression analyses. All tests were two-sided and a p-value < 0.05 was considered significant.

RESULTS

Total study population

Between January 2000 and December 2008, 1203 adults with isolated ASD (primum-, secundum- and sinus venosus defects) were registered with Concor. Of these, 71 patients (6%) were identified with PAH: 31 patients by RHC and 40 patients by echocardiography.[9, 15]

The majority of the patients with an ASD were female (63%). The sex-ratio did not differ between patients with or without PAH. A sinus venosus ASD was present significantly more often in PAH

patients. Furthermore, the time span of unrepaired ASD was longer in patients with PAH than those without PAH (Table 1).

Table 1. Demographics of patients with isolated ASD in the CONCOR registry 2000-2008

	Total N=1203	PAH N=71	Non-PAH N=1132
Female n (%)	754 (63)	50 (70)	704 (62)
Type of shunt n (%)			
ASD I	214 (18)	9 (13)	205 (18)
ASD II	621 (52)	45 (63)	576 (51)
Sinus Venosus	84 (7)	12 (17)#	72 (7)
undefined	282 (23)	5 (7)	277 (24)
Time span of unrepaired ASD (yrs)	32 ± 22	53 ± 21*	25 ± 20
Closure performed n (%)	794 (66)	44 (61)	750 (66)

(# p = 0.03,* p < 0.001), PAH = Pulmonary arterial hypertension, Non-PAH = Non-pulmonary arterial hypertension.

Case-control population

Three of the 71 patients with PAH were excluded because of insufficient data. In a case-control study, the remaining 68 patients with ASD and PAH were compared to 186 matched controls with ASD but without PAH (case-control population (CCP); figure 1). The median follow-up (years between time of ASD diagnosis and last visit) for the CCP was 5.5 years, ranging from 2.5-15.8 years (interquartile) and did not differ between the two groups (p = 0.79).

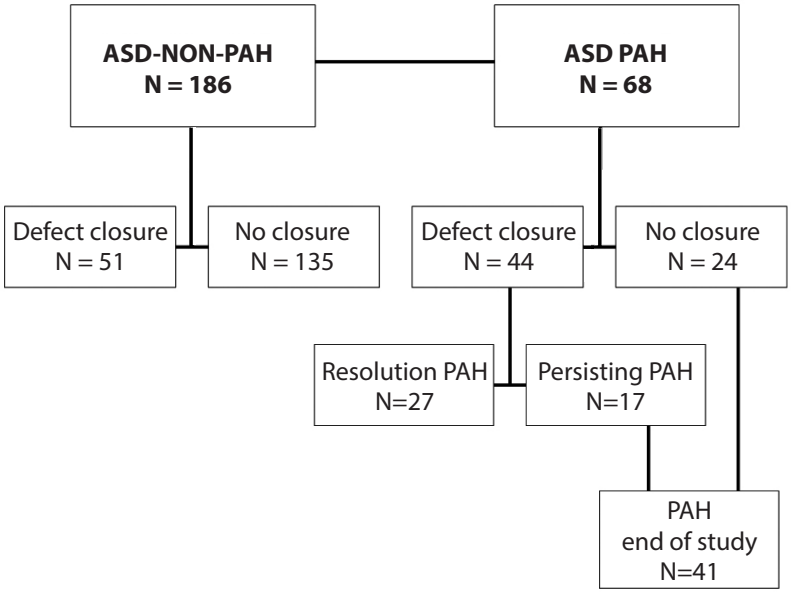

Figure 1. Population flow chart for the case-control population

Patient characteristics of the CCP are shown in Table 2. Patients with ASD and PAH had a larger defect, lower transcutaneous oxygen saturations and a higher functional class compared to those without PAH at the time of ASD diagnosis. NYHA classes are described in Table 4. In the ASD-PAH group, DNA samples were available for 56 of the 68 patients. *BMPR2* gene mutation analysis was performed for these 56 patients but no mutations were detected. Therefore, no further mutation analysis of the *BMPR2* gene was performed in the group of ASD patients without PAH.

Table 2. Patient characteristics of case-control population

N = 254		PAH N = 68		Non-PAH N = 186		p-Value*
Female n (%)		47 (69)		122 (66)		0.6
Time span of unrepaired ASD (yrs)		55 (34 – 72)		51 (38 – 61)		0.054
BMPR2 mutation	(n)	0	(56)	NT		
Size (mm)		24 (16 – 30)		18 (14 – 22)		0.003
Closure performed n (%)		44 (65)		134 (72)		0.26
Pre-operative hemodynamics						
<u>Echocardiography</u>						
sRVP (mm Hg)	(n)	54.5 (44.5 - 68.0)	(60)	31.0 (25.0 - 36.5)	(110)	< 0.001
<u>Heart catheterization</u>						
Saturation (%)	(n)	95.0 (94.0- 97.0)	(24)	97.0 (96.0- 98.0)	(79)	0.02
Qp/Qs	(n)	2.0 (1.8- 3.0)	(33)	2.0 (1.6- 2.6)	(89)	0.51
mPAP (mm Hg)	(n)	35.0 (30.0 - 45.0)	(33)	17.0 (14.0- 21.0)	(92)	< 0.001
sRVP (mm Hg)	(n)	55.0 (46.0 - 60.0)	(27)	32.0 (28.0- 37.0)	(88)	< 0.001
mWedge (mm Hg)	(n)	10.5 (6.0- 13.0)	(22)	8.0 (6.0- 10.0)	(76)	0.08
mRAP (mm Hg)	(n)	8.0 (5.0- 11.0)	(27)	5.0 (2.0 - 7.0)	(81)	< 0.001
PVR (Ru.m2)	(n)	4.7 (2.3- 7.1)	(18)	0.7 (0.5- 1.2)	(42)	< 0.001
CO (l/min)	(n)	7.1 (4.4- 8.4)	(16)	7.1 (5.7- 8.1)	(56)	0.46

Data presented as n (%) or median (interquartile range). *Mann-Whitney U test or Chi-Square test as appropriate. NT = not tested, PAH = Pulmonary arterial hypertension, Non-PAH = Non-pulmonary arterial hypertension, sRVP = systolic right ventricular pressure, Qp: Qs = ratio pulmonary flow: systemic flow, mPAP = mean pulmonary arterial pressure, mWedge = mean wedge pressure, mRAP = mean right atrium pressure, PVR = pulmonary vascular resistance, CO = cardiac output, T_{asd} = time at diagnosis ASD, n = number of patients for whom a specific parameter was available.

Of the 68 patients with ASD-PAH, 44 (65%) underwent defect closure (Figure 1). Pre-operative patient characteristics and hemodynamics are described in Table 3A. ASD-PAH patients who underwent defect closure had significantly lower pre-operative mPAP and PVR and higher pulmonary wedge pressure than those without defect closure.

Outcome

Resolution of PAH after defect closure

Of the 44 ASD-PAH patients with a closed defect, PAH subsequently resolved in 27 (61%) over a

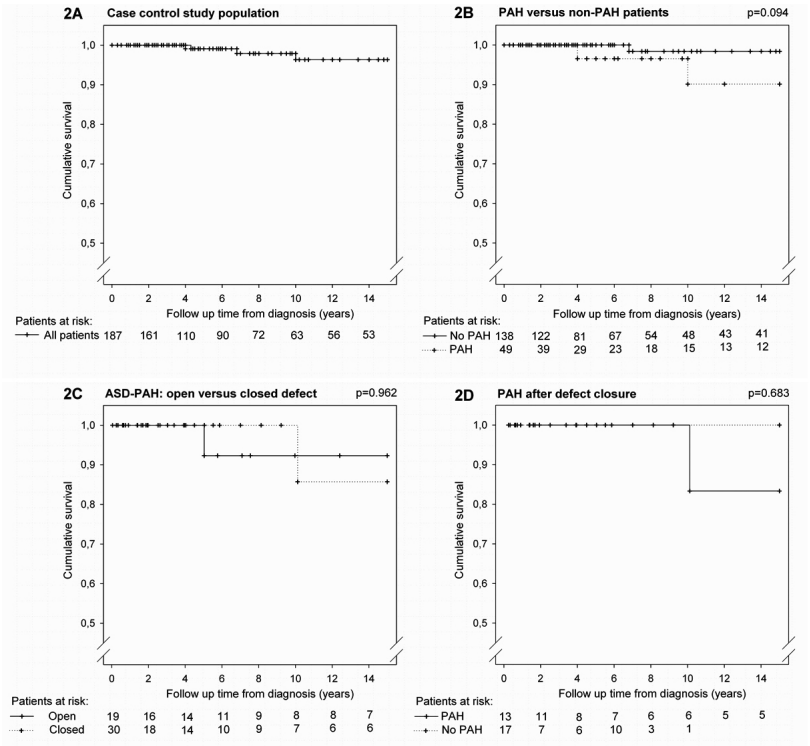

Figure 2. Cumulative survival curves. A) Cumulative survival of the case-control population. B) Cumulative survival of ASD-patients, stratified for the presence of PAH. C) Cumulative survival of ASD-PAH patients, stratified for closure or no-closure of the defect. D) Cumulative survival of ASD-PAH patients who underwent closure of the defect, stratified for resolution or persistence of PAH after closure.

median follow-up time after closure of 1.4 years (interquartile 0.7-5.0 yrs). In 17 patients (39%), PAH persisted after closure over a median follow-up time post-closure of 7.0 years (interquartile 3.9-25.4 yrs; p=0.008). We found no differences in pre-operative clinical characteristics or hemodynamics between patients with either resolving or persisting PAH (Table 3B).

Survival

The overall mortality in the case-control population was 2.4% (6/254) and was higher in patients with PAH (4/68 versus 2/186; $p < 0.05$). The cumulative survival curves were truncated at the 75 percentile follow-up time (15 years) because only a small number of patients had longer follow-up times. In all 254 patients with ASD, the 5 and 10 year survival rate was 99% and 96%, respectively (figure 2A). Patients with ASD and PAH had less favourable survival rates (5 and 10 years survival, 100% and 98%, respectively, versus 97% and 96% for ASD patients without PAH; $p = 0.09$; Figure 2B). No difference in survival was observed between PAH-patients with or without defect closure (5 and 10 years survival, 100% and 86%, respectively, versus 92% and 92% in patients without closure; p

Table 3A. Patient characteristics of our ASD-PAH population

N=68			No Closure N=24		Closure Defect N=44		p-Value
Female n (%)			14 (58)		33 (75)		0.16
Time span of unrepaired ASD (yrs)			58.5 (46.0-75.0)		55.0 (30.5-71.5)		0.15
ASD I	n (%)		4 (17)		5 (11)		0.54
ASD II	n (%)		16 (70)		30 (68)		0.90
Sinus venosus	n (%)		3 (13)		9 (21)		0.41
Undefined	n (%)		1 (4)		0 (0)		0.17
Size (mm)			26.0 (17.5-29.0)		24.0 (16.0-30.0)		0.69
Pre-operative hemodynamics							
Echocardiography							
sRVP (mm Hg)		(n)	63.5 (49.0 -80.5)	(24)	47.0 (41.5 -62.0)	(36)	0.045
Heart Catheterization							
Saturation (%)		(n)	93.5 (92.0-96.5)	(8)	95.0 (94.0-97.5)	(16)	0.17
Qp/Qs		(n)	1.8 (1.3-2.9)	(9)	2.2 (1.8-3.0)	(24)	0.29
mPAP (mm Hg)		(n)	42.0 (35.0-54.0)	(9)	33.0 (27.5-40.0)	(24)	0.06
sRVP		(n)	60.0 (53.0-74.0)	(9)	52.0 (46.0-58.0)	(18)	0.25
mWedge (mm Hg)		(n)	5.0 (5.0-5.0)	(5)	12.0 (10.0 -13.0)	(17)	0.001
mRAP (mm Hg)		(n)	10.0 (4.0-15.0)	(7)	7.5 (5.0-11.0)	(20)	0.40
CO (l/min)		(n)	7.0 (4.4-7.8)	(3)	7.2 (4.4-8.8)	(13)	0.77
PVR (Ru.m2)		(n)	7.0 (6.4-15.5)	(5)	3.2 (2.3-5.0)	(13)	0.05
PVR < 3 Ru.m2	median	(n)	0.2 (0.2 – 0.2)	(1)	1.8 (1.6-2.3)	(5)	0.04
PVR > 3 Ru.m2	median	(n)	11.3 (6.7-18.0)	(4)	4.9 (3.9-8.3)	(8)	0.04

Data presented as n (%) or Median (interquartile range). *Mann-Whitney U test or Chi-Square as appropriate. PAH = Pulmonary arterial hypertension, Non-PAH = Non Pulmonary arterial hypertension, sRVP = systolic right ventricular pressure, Qp: Qs = ratio pulmonary flow: systemic flow, mPAP = mean pulmonary arterial pressure, mWedge = mean wedge pressure, mRAP = mean right atrium pressure, PVR = pulmonary vascular resistance CO = cardiac output, T_{asd} = time at diagnosis ASD, n = number of patients for whom a specific parameter was available.

= 0.96; Figure 2C). In the ASD-PAH patients with ASD closure and resolving PAH, the 5 and 10 years survival was 100% and 100% and with persisting PAH 100% and 83% (p = 0.68; Figure 2D).

In a univariate Cox regression analysis in the CCP, death was associated with ASD size and age at ASD diagnosis (hazard risk (HR) 1.298 (95% CI 1.01-1.669), p = 0.041 and HR 1.192 (95% CI 1.017-1.397), p = 0.030, respectively) but not with pre-operative hemodynamic parameters.

Functional class

NYHA functional class (NYHA-FC) was assessed at the time of ASD diagnosis, and at the last follow-up visit. The functional class of ASD-patients with PAH was worse than those without PAH, both at time of ASD diagnosis (p < 0.001), and at last visit (p = 0.04; Table 4). The NYHA-FC improved significantly after defect closure, both in patients without PAH (p < 0.001) and those with PAH (p < 0.001) (Table 4). In patients with PAH, this improvement after defect closure was independent of

Table 3B. Patient characteristics of ASD-PAH patients who underwent defect closure, with or without subsequent resolution of PAH

N=44	Resolution PAH+ closure N=27	Persistent PAH+ closure N=17	p-value
Female n (%)	20 (74)	13 (77)	0.86
Time span of unrepaired ASD (yrs)	55.0 (31.0-72.0)	55.0 (28.0 – 70.0)	0.77
Type ASD I n (%) ASD II n (%) Sinus venosus n (%)	 2 (7.4) 19 (70.4) 6 (22.2)	 3 (17.6) 11 (64.7) 3 (17.6)	 0.30 0.69 0.71
Size of ASD (mm)	24.0 (17.0 – 32.0)	19.0 (14.0-30.0)	0.49
Pre-operative hemodynamics Echocardiography sRVP (mm Hg) (n)	 45.0 (41.0-59.0) (25)	 56.0 (48.0 – 85.0) (11)	 0.037
Heart catheterization Saturation (%) (n) Qp/Qs (n) mPAP (mm Hg) (n) sRVP (mm Hg) (n) mWedge (mm Hg) (n) mRAP (mm Hg) (n) CO(l/min) (n) PVR (Ru.m2) (n) PVR < 3 Ru.m2 (n) PVR > 3 Ru.m2 (n)	 95.0 (94.0 - 97.0) (9) 2.2 (1.8 - 3.0) (13) 32.0 (27.0 - 36.0) (13) 55.0 (46.0 - 59.0) (9) 11.0 (10.0 - 13.0) (9) 10.0 (7.0 – 11.0) (11) 7.6 (4.6 – 9.6) (8) 2.7 (2.0 – 4.1) (8) 2.0 (1.5 – 2.3) (4) 4.1 (3.1 - 8.0) (4)	 95.0 (95.0 - 98.0) (7) 2.6 (1.8 - 3.0) (11) 34.0 (30.0 - 41.0) (11) 51.0 (46.0 - 57.0) (9) 12.5 (8.5 - 14.0) (8) 6.0 (5.0 – 7.0) (9) 6.2 (4.4 – 7.8) (5) 4.8 (4.5 – 7.1) (5) 1.6 (1.6-1.6) (1) 6.0 (4.7 – 8.3) (4)	 0.64 0.82 0.96 0.52 0.88 0.17 0.39 0.33 0.86 0.63

Data presented as n (%) or median (interquartile range). *Mann-Whitney U test or Chi-Square test as appropriate. PAH = Pulmonary arterial hypertension, Non-PAH = Non-pulmonary arterial hypertension, sRVP = systolic right ventricular pressure, Qp: Qs = ratio pulmonary flow: systemic flow, mPAP = mean pulmonary arterial pressure, mWedge = mean wedge pressure, mRAP = mean right atrium pressure, PVR = pulmonary vascular resistance. CO = cardiac output, T_{asd} = time at diagnosis ASD, n = number of patients for whom a specific parameter was available.

whether or not the PAH resolved after closure.

In this study, no patient, irrespective of pulmonary vascular resistance (PVR), was pre-treated with targeted PAH therapy. At the end of the study, 14/41 patients with PAH, with both open and closed defects, were using targeted PAH therapy: 8/25 patients had an unrepaired ASD (32%), and 6/16 patients (37.5%) had a closed ASD.

Table 4. NYHA functional class at diagnosis and at follow-up

Study population n=254	ASD-non-PAH n=183		ASD-PAH n=68		
	open no PAH N=52	**closed no PAH** N=131	**open PAH** N=24	**closed resolution PAH** N=27	**closed persisting PAH** N=17
NYHA T_{ASD*}					
I	34	50	3	9	1
II	7	35	6	7	2
III	0	17	9	10	8
IV	0	1	5	1	0
Missing	11	28	1	0	6
NYHA T_{End}					
I	12	86	2	14	8
II	3	13	2	3	0
III	0	2	1	1	2
IV	0	0	1	0	0
Missing	37	30	18	9	7
Follow-up (yrs) (T_{End} - T_{ASD})	4.0 (1.9 – 9.7)	5.4 (2.4 – 16.7)	7.5 (3.0 - 23.1)	1.4 (0.7 – 5.0)	7.0 (3.9 – 24.4)
Age ASD	41.0 (30.0-58.0)	45.5 (32.0 – 56.5)	44.0 (24.0 - 66.0)	49.0 (29.0 - 68.0)	52.0 (40.0 - 66.0)
Death n (%)	0	2 (1.5)	1 (4.2)	0	3 (17.6)

PAH = Pulmonary arterial hypertension, Non-PAH = Non-pulmonary arterial hypertension, NYHA = New York Heart Association (functional) class, T_{ASD} = time at diagnosis ASD, T_{end} = time at last visit.

DISCUSSION

In this nationwide cohort study of adult patients with ASD, the prevalence of associated PAH was 6%, which is lower than previously reported.[2, 7-10, 18] Earlier diagnosis, the current treatment strategy of early ASD-repair and less selection bias in the national cohort studies are the most likely reasons for the lower prevalence of ASD-associated PAH seen in our study. Clinical risk factors for the development of PAH identified in this cohort included the sinus venosus type defect, the size of the defect, and the length of time an unrepaired ASD had been present. These agree with risk factors identified in previous, smaller, studies.[6, 9, 13, 18] In contrast to previous reports, gender and the presence of a *BMPR2* mutation were not identified as risk factors in our study.[19, 20] Increased individual genetic susceptibility due to the presence of a *BMPR2* mutation has been suggested as risk factor for the development of PAH in ASD patients, as mutations in *BMPR2* are associated with idiopathic and heritable PAH in about 20% and 70% of cases, respectively.[21, 22] However, the role of *BMPR2* mutations in PAH associated with congenital heart disease has thus far been unclear, with contradictory data coming from the small patient numbers studied.[12, 23] Our study found no *BMPR2*

mutations in a cohort of 56 adult patients with ASD and associated PAH, and thereby demonstrates that these mutations do not play a role in the development of PAH in ASD patients.

Early closure of a hemodynamically significant ASD prevents the development of PAH, RVF and arrhythmias. However, when an ASD is diagnosed later in life and PAH is already present, it is not yet clear how best to treat it. There is expert consensus that patients with Eisenmenger syndrome, in which the shunt through the ASD has reversed into a right-to-left shunt, have a worse prognosis after defect closure. In such patients, the ASD might serve as a pop-off valve, reducing or postponing RVF. Most patients with ASD and associated PAH do not present with Eisenmenger syndrome, but have sub-systemic pulmonary vascular resistance and predominantly a left-to-right shunt. ASD closure in these patients has been suggested to be beneficial at short-term follow-up, focussing on a decrease in pulmonary arterial pressure,[18] although concerns remain about the potential progression of PAH in the longer term. PAH-targeted drug therapy offers the opportunity of both pre-treatment before defect closure and treatment of persisting PAH after closure. The effect of either strategy on outcome, however, is still unclear. Our current knowledge is insufficient to identify adequately whether patients with ASD-PAH will benefit from defect closure or will still deteriorate in the long term after closure.

Almost 25 years ago, Steele et al. identified PVR to be the best predictor of surgical outcome and advised it only in patients with a PVR less than 15 WU.m2. Furthermore, in patients with borderline PVR, the systemic arterial oxygen saturation was suggested to predict surgical outcome.[24] In contrast, patients with ASD-PAH in the present study who underwent ASD closure had significantly lower PVR (median 3.3 WU.m2) than the cut-off value advised by Steele et al. Nevertheless, at a median follow-up of seven years after closure, more than one-third of the ASD-PAH patients showed persistent PAH, suggesting that other unidentified determinants play a role in the persistence or resolution of PAH. Our study revealed no pre-operative characteristics that were associated with postoperative PAH-resolution. Acute pulmonary vasodilator tests, with inhaled nitric oxide or other agents, have been previously suggested to predict the reversibility of pulmonary vascular disease after defect closure.[25] Unfortunately, the data on acute pulmonary vasodilator response available in this study were insufficient to assess this effect.

Irrespective of the persistence or resolution of PAH, ASD closure resulted in improvement of the NYHA functional class in all ASD-PAH patients. This observation is in agreement with the experience of Humenberger et al.[18] However, a decreased volume loading of the right ventricle and an improved left ventricular output may be responsible for this beneficial feature, rather than real improvement in the pulmonary vascular disease.[26-28] Although a decrease in pulmonary artery pressure soon after ASD closure is regarded as a successful outcome by some authors, this criterion may be misleading: a reduction in increased pulmonary blood flow will also lead to a decrease of pulmonary artery pressure in patients with advanced pulmonary vascular disease.[28] In these patients, pulmonary artery pressure will gradually increase in the long-term, in parallel with the progression of the vascular disease and the eventual outcome will be worse than that for patients

with an open defect.[2, 28] Unfortunately, the small patient numbers in our study did not allow us to draw firm conclusions about this aspect of the problem.

Study limitations

The retrospective nature of this study comes with inherent limitations. The initial diagnosis of PAH was confirmed with RHC in 60% of the patients, whereas PAH in the remaining patients was defined by echocardiography using previously defined criteria. Echocardiography was also used for to assess PAH after defect closure. However, the large population cohort outweighs this limitation, since limiting inclusion to only RHC-confirmed patients would introduce selection bias, impeding accurate estimates of prevalence. Missing data and relatively small patient numbers after stratification, despite our large cohort of 1203 ASD patients, also limited the extent of risk factor analyses in specific subgroups.

CONCLUSIONS

In this Dutch cohort of patients with isolated ASD, the prevalence of PAH was 6%. Clinical risk factors for the occurrence of PAH were sinus venosus type defect, larger size of the defect, and longer time span in which an unrepaired ASD had been present, but gender was not a risk factor. Further, *BMPR2* mutations could not be identified as a risk factor for PAH in patients with ASD. Although patients with ASD and PAH who underwent defect closure had only moderately elevated PVR, more than one-third of patients showed persistent PAH years after the closure. Pre-operative clinical and hemodynamic characteristics did not predict the resolution or persistence of PAH after closure. Nevertheless, the functional class improved in all patients after closure of their ASD irrespective of the pre-operative presence or postoperative persistence of PAH. The role of persisting PAH after ASD closure could not be determined in this study, and it remains a serious concern.

REFERENCES

1. Campbell M, Neill C, Suzman S. The prognosis of atrial septal defect. *Br Med J*. 1957;1(5032):1375-1383.
2. Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. *Circulation*. 1968;37(5):805-815.
3. Losay J, Rosenthal A, Castaneda AR, Bernhard WH, Nadas AS. Repair of atrial septal defect primum. Results, course, and prognosis. *J Thorac Cardiovasc Surg*. 1978;75(2):248-254.
4. Meijboom F, Hess J, Szatmari A, et al. Long-term follow-up (9 to 20 years) after surgical closure of atrial septal defect at a young age. *Am J Cardiol*. 1993;72(18):1431-1434.
5. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21-33 years. *Eur Heart J*. 2003;24(2):190-197.
6. Webb G, Gatzoulis MA. Atrial septal defects in the adult: Recent progress and overview. *Circulation*. 2006;114(15):1645-1653. doi: 10.1161/CIRCULATIONAHA.105.592055.
7. Brooks WD. Pulmonary hypertension with pulmonary regurgitation possibly due to interatrial septal defect. *Proc R Soc Med*. 1942;35(3):191-192.

8. Campbell M. Natural history of atrial septal defect. *Br Heart J*. 1970;32(6):820-826.

9. Engelfriet P, Meijboom F, Boersma E, Tijssen J, Mulder B. Repaired and open atrial septal defects type II in adulthood: An epidemiological study of a large European cohort. *Int J Cardiol*. 2008;126(3):379-385. doi: 10.1016/j.ijcard.2007.04.044.

10. Sachweh JS, Daebritz SH, Hermanns B, et al. Hypertensive pulmonary vascular disease in adults with secundum or sinus venosus atrial septal defect. *Ann Thorac Surg*. 2006;81(1):207-213. doi: 10.1016/j.athoracsur.2005.07.053.

11. Vogel M, Berger F, Kramer A, Alexi-Meshkishvili V, Lange PE. Incidence of secondary pulmonary hypertension in adults with atrial septal or sinus venosus defects. *Heart*. 1999;82(1):30-33.

12. Therrien J, Rambihar S, Newman B, et al. Eisenmenger syndrome and atrial septal defect: Nature or nurture? *Can J Cardiol*. 2006;22(13):1133-1136.

13. Yong G, Khairy P, De Guise P, et al. Pulmonary arterial hypertension in patients with transcatheter closure of secundum atrial septal defects: A longitudinal study. *Circ Cardiovasc Interv*. 2009;2(5):455-462. doi: 10.1161/CIRCINTERVENTIONS.108.826560.

14. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: Rationale, design, and first results. *Eur J Epidemiol*. 2005;20(6):549-557.

15. Duffels MG, Engelfriet PM, Berger RM, et al. Pulmonary arterial hypertension in congenital heart disease: An epidemiologic perspective from a Dutch registry. *Int J Cardiol*. 2007;120(2):198-204. doi: 10.1016/j.ijcard.2006.09.017.

16. Hayes VM, Wu Y, Osinga J, et al. Improvements in gel composition and electrophoretic conditions for broad-range mutation analysis by denaturing gradient gel electrophoresis. *Nucleic Acids Res*. 1999;27(20):e29.

17. Wu Y, Hayes VM, Osinga J, et al. Improvement of fragment and primer selection for mutation detection by denaturing gradient gel electrophoresis. *Nucleic Acids Res*. 1998;26(23):5432-5440.

18. Humenberger M, Rosenhek R, Gabriel H, et al. Benefit of atrial septal defect closure in adults: Impact of age. *Eur Heart J*. 2011;32(5):553-560. doi: 10.1093/eurheartj/ehq352; 10.1093/eurheartj/ehq352.

19. Sanchez O, Marie E, Lerolle U, Wermert D, Israel-Biet D, Meyer G. Pulmonary arterial hypertension in women. *Rev Mal Respir*. 2010;27(8):e79-87. doi: 10.1016/j.rmr.2009.12.001; 10.1016/j.rmr.2009.12.001.

20. Manes A, Palazzini M, Dardi F, D'Adamo A, Rinaldi A, Galie N. Female gender and pulmonary arterial hypertension: A complex relationship. *G Ital Cardiol (Rome)*. 2012;13(6):448-460. doi: 10.1714/1073.11764; 10.1714/1073.11764.

21. Aldred KJ, McPherson SA, Wang P, et al. Drug interactions with bacillus anthracis topoisomerase IV: Biochemical basis for quinolone action and resistance. *Biochemistry*. 2012;51(1):370-381. doi: 10.1021/bi2013905.

22. Machado RD, Eickelberg O, Elliott CG, et al. Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(1 Suppl):S32-42. doi: 10.1016/j.jacc.2009.04.015.

23. Roberts KE, McElroy JJ, Wong WP, et al. BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. *Eur Respir J*. 2004;24(3):371-374. doi: 10.1183/09031936.04.00018604.

24. Steele PM, Fuster V, Cohen M, Ritter DG, McGoon DC. Isolated atrial septal defect with pulmonary vascular obstructive disease--long-term follow-up and prediction of outcome after surgical correction. *Circulation*. 1987;76(5):1037-1042.

25. Berger RM. Possibilities and impossibilities in the evaluation of pulmonary vascular disease in congenital heart defects. *Eur Heart J*. 2000;21(1):17-27. doi: 10.1053/euhj.1999.1698.

26. Balint OH, Samman A, Haberer K, et al. Outcomes in patients with pulmonary hypertension undergoing percutaneous atrial septal defect closure. *Heart*. 2008;94(9):1189-1193. doi: 10.1136/hrt.2006.114660.

27. Salehian O, Horlick E, Schwerzmann M, et al. Improvements in cardiac form and function after transcatheter closure of secundum atrial septal defects. *J Am Coll Cardiol*. 2005;45(4):499-504. doi: 10.1016/j.jacc.2004.10.052.

28. Berger RM, Pricker K, Hoendermis ES, Bartelds B. Percutaneous atrial septal defect closure in patients with pulmonary hypertension. *Heart*. 2008;94(12):1653; author reply 1653-4.